Bayer HealthCare
Pharmaceuticals
USA

Magnevist

(Gadopentetate dimeglumine)

Joint Meeting of the Cardiovascular and Renal Drugs and Drug Safety and Risk Management Advisory Committee

Gaithersburg, MD, December 8, 2009

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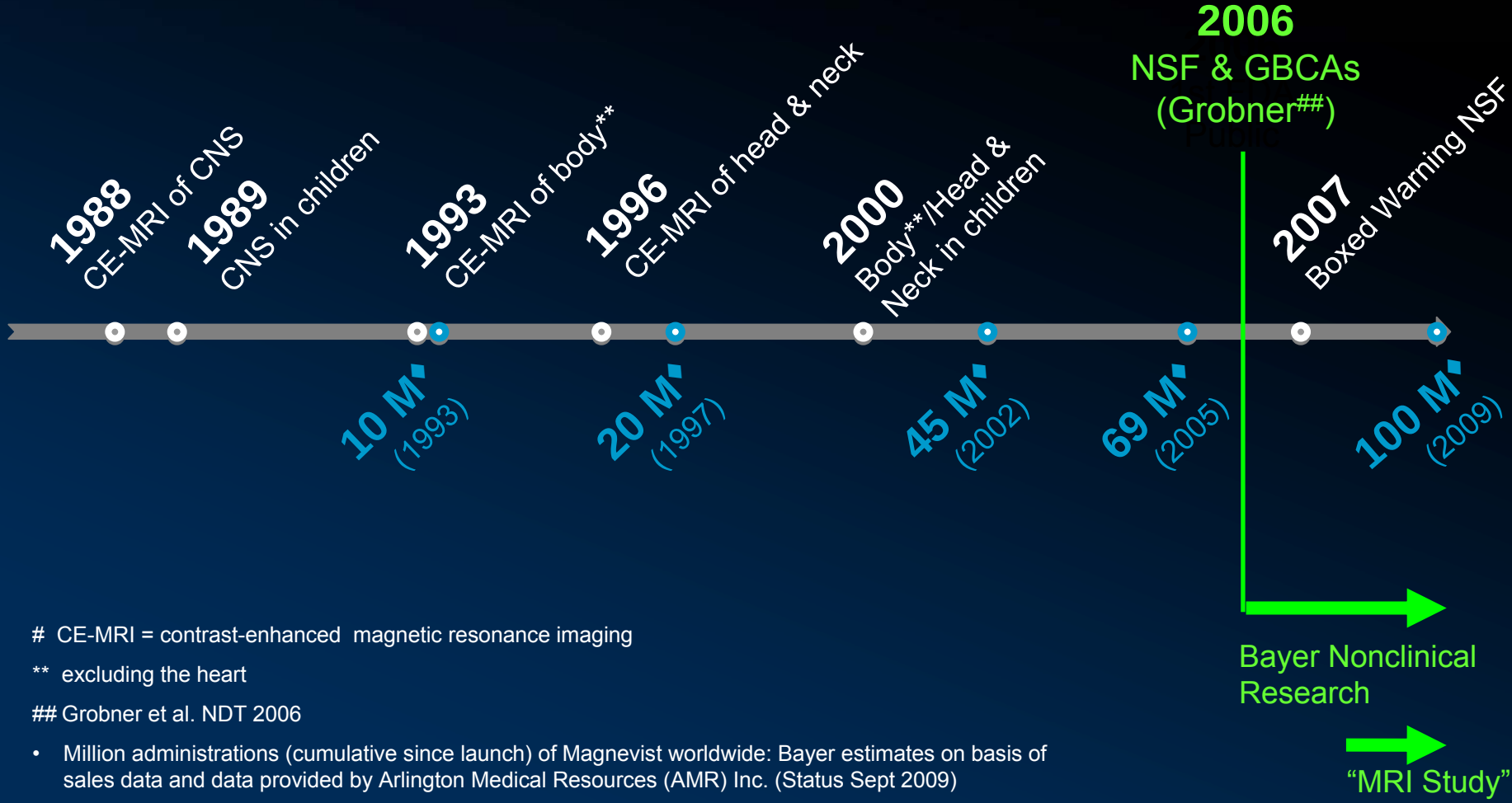
Agenda

- Magnevist – Introduction
- Summary of Nonclinical NSF Research Results
- Magnevist & NSF – Summary of Clinical Evidence
- NSF Risk Mitigation Activities
- Summary

Magnevist:
Development and Post-Approval Events in US



CE-MRI = contrast-enhanced magnetic resonance imaging

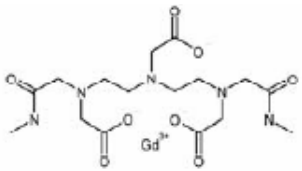
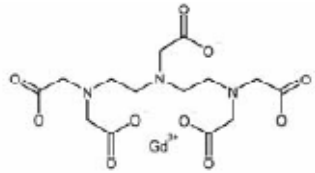
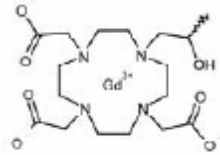
** excluding the heart

Grobner et al. NDT 2006

- Million administrations (cumulative since launch) of Magnevist worldwide: Bayer estimates on basis of sales data and data provided by Arlington Medical Resources (AMR) Inc. (Status Sept 2009)

Summary of Nonclinical NSF Research Results

Marketed GBCAs Can be Divided Into Three Categories

Non-ionic linear	Ionic linear	Macrocyclic
		
Omniscan™ Optimark™	**Magnevist®** MultiHance® Eovist® Ablavar™	ProHance® (Dotarem®) (Gadovist®)

Decreasing Gd Release *(in vitro)**

Magnevist® Gadovist® and Eovist® is a trademark of Bayer. All other trademarks are the property of their respective owners

*Frenzel et al. Investigative Radiology Dec 2008

Results of Nonclinical Research

- Gd release observed in human serum in vitro was highest from linear non-ionic GBCAs, lower from linear ionic GBCAs, and lowest from macrocyclic GBCAs.
- Gd retention observed in rat skin was higher after administration of linear non-ionic GBCAs than after linear ionic GBCAs, and lowest after macrocyclic GBCA administration.
- Only non-ionic linear GBCAs induced NSF-like skin lesions in some study rats.

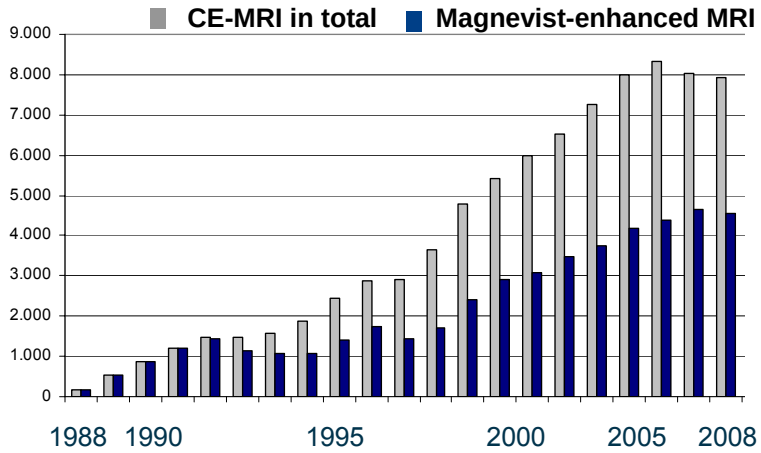
→ Caution should be exercised when extrapolating results to humans.

Magnevist & NSF – Summary of Clinical Evidence

Magnevist is the Most Widely Used and Studied MRI Contrast Agent

- Approved* for use in CE-MRI# in a broad range of indications and patients
- Studied in > 11,000 subjects in clinical trials worldwide
- Cited in > 16,000 scientific publications
- Administered an estimated total of > 100 million times worldwide since launch

US CE-MRI Administrations and Magnevist share (in thousands)*



*** Source:** Bayer estimates on basis of sales data and data provided by Arlington Medical Resources (AMR) Inc. (Status Sep 2009)

* US Package Insert (Please note: range of approved indications and dosages may vary across countries.)

CE-MRI = contrast-enhanced magnetic resonance imaging

Observational Studies Do Not Allow Robust Conclusions on Differential Risk of GBCAs

- No adequate observational studies or randomized clinical trials have compared the risk of NSF among available GBCAs.
- The only study that compared the risk of NSF among GBCAs reported a significantly higher risk (OR=13.17 [95% CI: 4.6-37.2]) with Omniscan than with Magnevist*.
  - However, this study did not adjust for many important confounding variables (e.g., dose, indication, number of patients at risk receiving GBCAs, number of procedures per patient).

* Wertman et al. Radiology 2008 (248) 3:799-806

Number of NSF Reports Needs to be Considered in the Context of Overall Usage of GBCAs

Gd-based contrast agent	Categories of GBCA	Estimated total administrations since approval (in millions, US only)*	Number of US reports according to AERS** (all reports)	
Omniscan	Nonionic	> 25.0	929	
Optimark	Nonionic	> 2.5	427	
Magnevist	**Ionic**	**> 50.0**	**654**	
MultiHance	Ionic	> 2.5	335	
ProHance	Macrocyclic	> 7.5	325	

* Bayer estimates on basis of sales data and data provided by Arlington Medical Resources (AMR) Inc. (Status Sep 2009)

** *Joint Meeting of the Cardiovascular and Renal Drugs and Drug Safety and Risk Management Advisory Committee Gadolinium-Based Contrast Agents & Nephrogenic Systemic Fibrosis, FDA Briefing Document, p 23*

Number of NSF Reports Needs to be Considered in the Context of Overall Usage of GBCAs

Gd-based contrast agent	Date of US approval	Estimated total administrations since approval (in millions, US only)*	Number of US reports according to AERS** (all reports)	Number of US reports according to AERS (only one GBCA administered)
Omniscan	1993	> 25.0	929	382
Optimark	1999	> 2.5	427	35
Magnevist	**1988**	**> 50.0**	**654**	**195**
MultiHance	2004	> 2.5	335	1
ProHance	1992	> 7.5	325	0

* Bayer estimates on basis of sales data and data provided by Arlington Medical Resources (AMR) Inc. (Status Sep 2009)

** *Joint Meeting of the Cardiovascular and Renal Drugs and Drug Safety and Risk Management Advisory Committee Gadolinium-Based Contrast Agents & Nephrogenic Systemic Fibrosis, FDA Briefing Document, p 23*

Comparisons of NSF Risk Among Early-Entry and Recent-Entry GBCAs May be Difficult to Interpret

1. GBCAs with recent-market entry are likely to be used in patients exposed to older GBCAs, especially those with dominant market share.
2. Analyses that focus on “unconfounded” cases and exclude cases involving multiple GBCAs are likely to yield a biased underestimate of NSF risk among recent-entry agents.
3. Analyses that focus on “unconfounded” cases ignore available information regarding the temporal proximity of a recently-used GBCA and the development of NSF.
4. Recently-approved GBCAs have been used in an environment of heightened awareness of NSF risk, and thus, their use is likely to have been directed towards low-risk patients.

AERS Data Mining Analysis: Non-ionic Linear GBCAs Have the Highest Reporting Ratios

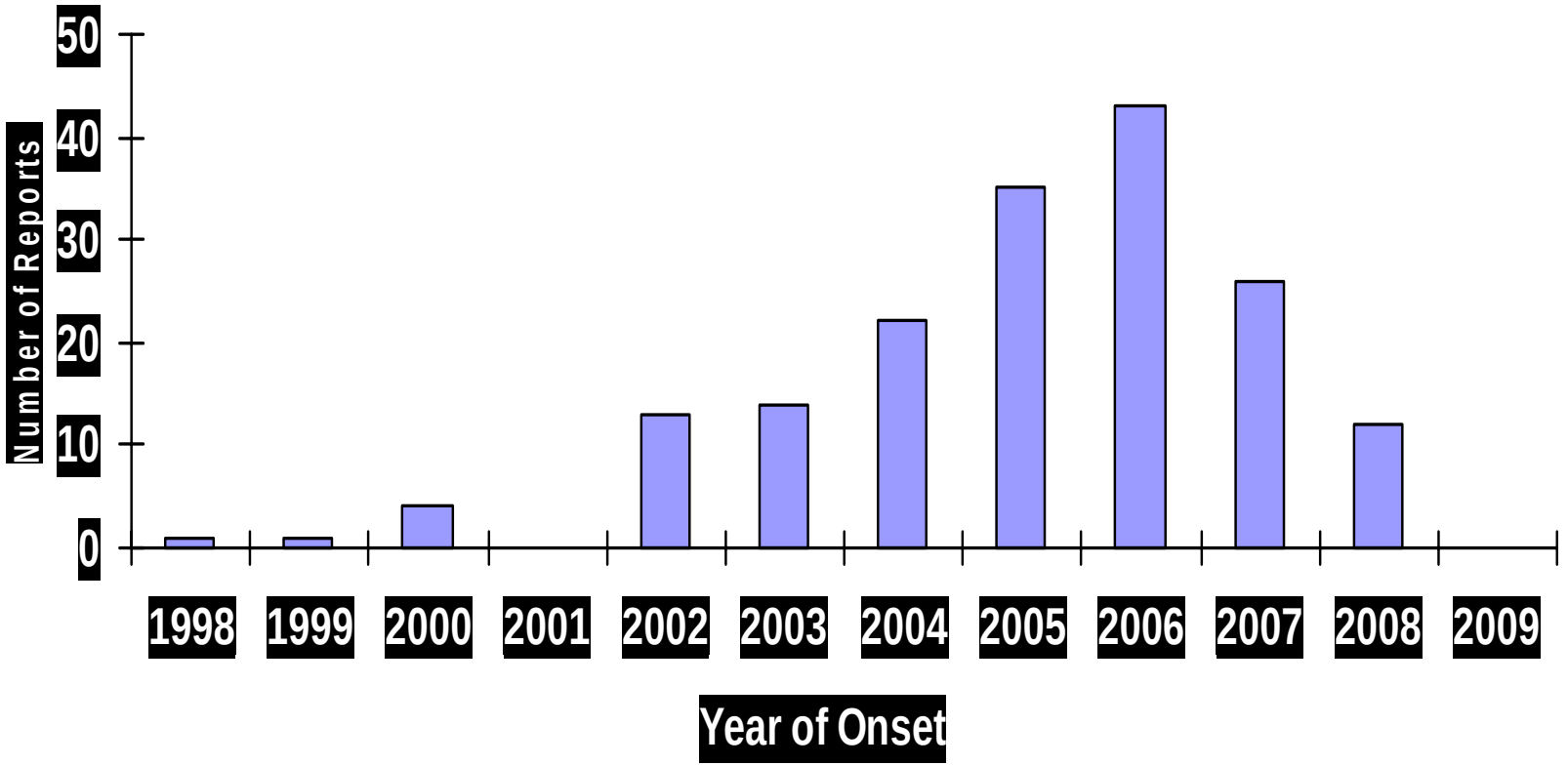
GBCA	Date of US approval	Estimated total administrations to date (in millions,US only)	Proportional reporting ratio	Relative reporting ratio
Magnevist	1988	> 50.0	0.780	0.888
ProHance	1992	> 7.5	0.021	0.027
Omniscan	**1993**	**> 25.0**	**7.192**	**4.537**
Optimark	**1999**	**> 2.5**	**5.406**	**5.109**
MultiHance	2004	> 2.5	0.064	0.071

NSF Risk Mitigation Activities

Current Risk Mitigation Activities Have Been Effective in Markedly Reducing Reports of NSF

Occurrence of NSF has decreased over the last three years:

Date of Onset of Symptoms Suggestive of NSF in Reports with Documented Magnevist Administration and Known Onset Date (Status Sep 30, 2009)



MRI Study ("Magnevist in Renally Impaired Patients")

Study objective	Prospective observational study to assess the magnitude of risk with the administration of Magnevist for the development of nephrogenic systemic fibrosis (NSF) based on diagnostically specific clinical and histopathologic information
Patient population	1000 patients with moderate (approx. 600) to severe (approx. 400) renal impairment
Participating country	US
Number of active sites	18
First patient/First visit	November 2008
Enrollment status (Sep 2009)	57 patients; 42 in follow-up (39 moderate, 3 severe renal impairment)

Magnevist - Summary

- Nonclinical studies suggest a lower NSF risk for ionic linear GBCAs (e.g. Magnevist) and macrocyclic GBCAs as compared with non-ionic linear GBCAs (e.g. Omniscan, Optimark).
- Clinical data (from spontaneous reporting and observational studies) indicate a lower NSF risk for Magnevist as compared with non-ionic agents, such as Omniscan and Optimark.
- No data from clinical studies has yielded evidence for reliable differences in NSF risk between Magnevist and other ionic linear (e.g. MultiHance) or macrocyclic GBCAs.
- Focusing risk assessment on the frequency of spontaneous "unconfounded" (single agent) reports is likely to yield biased risk estimates among recently-approved GBCAs.
- Current class labeling and awareness of NSF risk factors appear to have nearly eliminated occurrence of new cases of NSF.